International Journal of Infectious Diseases 29 (2014) 194–196

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

Rickettsia africae infection complicated with painful sacral syndrome in an Italian traveller returning from Zimbabwe

Lorenzo Zammarchi [a], Alberto Farese [b], Michele Trotta [b], Aldo Amantini [c], Didier Raoult [d], Alessandro Bartoloni [a,b,*]

[a] *Clinica Malattie Infettive, Dipartimento di Medicina Sperimentale e Clinica, Università Degli Studi di Firenze, Largo Brambilla 3, 50134 Firenze, Italy*
[b] *SOD Malattie Infettive e Tropicali, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy*
[c] *SODc Neurofisiopatologia, DAI Neuroscienze, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy*
[d] *Unité des Rickettsies, Faculté de Médecine, Marseille, France*

ARTICLE INFO

Article history:
Received 20 August 2014
Received in revised form 30 September 2014
Accepted 2 October 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Rickettsia africae
Neurological complication
Painful sacral syndrome
Pain
Travel

SUMMARY

We report a case of *Rickettsia africae* infection complicated with painful sacral syndrome in an Italian traveller returning from Zimbabwe. The patient presented with fever, a tache noire on the left leg, and a neurological syndrome characterized by severe pain of the left leg, predominantly located in the left dorsal thigh and radiating to the calf; she had urinary retention and faecal incontinence. The diagnosis of *R. africae* was confirmed by polymerase chain reaction on a skin biopsy. The severe left leg pain persisted despite a complete course of doxycycline. A 4-month course of corticosteroids and the addition of carbamazepine was needed to achieve the control of pain. This case highlights the possibility of severe manifestations of *R. africae* infection and the possibility of a complex pathogenesis of the neurological syndrome, due perhaps to both the direct damage induced by *R. africae* and an immune-mediated mechanism.

1. Introduction

Rickettsia africae, a member of the spotted fever group rickettsiae, is the aetiological agent of African tick bite fever (ATBF), an emerging disease described in travellers returning from Africa and the French West Indies.[1] ATBF is transmitted by ticks of the *Amblyomma* genus and is usually considered a benign disease.[1]

We report a case of *R. africae* infection complicated with painful sacral syndrome diagnosed in an Italian traveller returning from Zimbabwe.

2. Case report

In March 2014, a 40-year-old Italian woman was admitted to the Hospital of Rimini, Italy, because of a 2-week history of severe pain in the left leg, predominantly located in the left dorsal thigh and radiating to the calf. She also had a 1-day history of intense pelvic pain, rectal tenesmus, and faecal incontinence. She denied any sensory disturbances.

The patient had returned a week before from Zimbabwe, where she worked for 3 weeks as a medical doctor in a missionary hospital in a rural area. Symptoms had started while she was in Zimbabwe and were preceded by prodromal symptoms such as fatigue, headache, and nausea for 2 days. The patient reported that, by the time of symptoms onset, some non-painful, non-pruritic papular lesions were present on the left lower limb and a vesicular lesion on the left popliteal fossa.

Physical examination revealed a black crusted lesion on the external malleolus (Figure 1), fever (38 °C), urinary retention that was resolved with an indwelling catheter (900 ml of clear urine was obtained), a hypertonic anal sphincter, and oedema of the right hemi-vulva. Tendon reflexes were present and symmetrical except for a slight reduction of the left Achilles reflex. The plantar reflex was normal bilaterally. Segmental strength was normal and symmetrical. No sensory loss of the lower limb was observed, including the perineal region. No paresthesia/dysesthesia was reported by the patient. The Lasègue sign was positive on the left side. The spontaneous radiating pain with

* Corresponding author. Tel./fax: +39 055 7949431.
E-mail address: alessandro.bartoloni@unifi.it (A. Bartoloni).

http://dx.doi.org/10.1016/j.ijid.2014.10.017

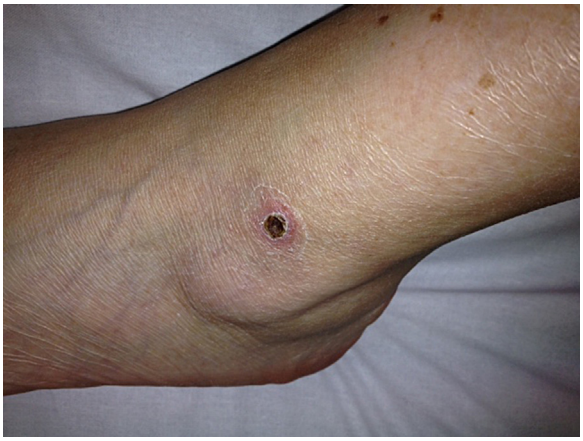

Figure 1. Cutaneous black crusted lesion on the left external malleolus, compatible with *"tache noire"*.

paroxysmal exacerbation mainly involved the S1–S2 sensory distribution. Blood tests were normal except for mild leukocytosis (10.6×10^9 leukocytes/l, 76.1% neutrophils) and thrombocytosis (411×10^9 platelets/l). Thick and thin blood smears and antigen immunochromatographic testing for malaria were negative.

Motor evoked potentials for the four limbs were normal, and cortical somatosensory evoked potentials from stimulation of the tibial nerve at the ankle and dorsal clitoral nerve were normal. The plantar sympathetic skin response was normal and symmetrical. The motor nerve conduction velocity and sensory nerve conduction velocity were normal for the lower limbs, with normal amplitude of the compound muscle action potential and sensory nerve action potential. The soleus H-reflex was of normal latency bilaterally, but with a significant amplitude reduction on the left (H/M amplitude less than 50%). Electromyography of the external anal sphincter showed sporadic spontaneous motor unit activity on the left and a bilateral reduction of voluntary activity, which was more evident on the left. The neurological assessment indicated a mild asymmetric involvement of sacral S1–S2–S3 tracts, more evident on the left side. An abdominal computed tomography scan showed the presence of impacted stool in the rectum. Cerebrospinal fluid and spinal cord magnetic resonance imaging were normal.

The patient was treated empirically with doxycycline for 20 days (100 mg, twice daily) and methyl prednisolone for 4 days (initial dose of 40 mg, twice daily), which was then tapered over a 2-month period. The patient also received pregabalin (75 mg, twice daily) and oxycodone/naloxone (5 mg/2.5 mg, three times daily) for pain control. Anal hypertonia was treated with anal dilators and nifedipine/lidocaine ointment.

Serology for *Borrelia burgdorferi* (ELISA), human T-lymphotropic virus 1 and 2, HIV, Schistosoma, *Treponema pallidum*, hepatitis B virus, and hepatitis C virus were all negative. Serology for *Rickettsia rickettsii/typhi* (indirect immunofluorescence, IFA) on day 18 following symptoms onset was IgG-positive (IgG >1:512, positive reference value >1:256) and IgM-positive (qualitative result). A week after admission, the patient was transferred to the Tuscany Reference Centre for Tropical Diseases, Infectious and Tropical Diseases Unit, Azienda Ospedaliero Universitaria Careggi, Florence, Italy, where the diagnosis of rickettsiosis was confirmed with serology (*Rickettsia conorii* IgG IFA >1:2048, positive reference value >1:64) on day 30 after symptoms onset. Serum and whole blood samples, and a biopsy of the black crusted lesion that was compatible with a 'tache noire', taken on day 30 following symptoms onset, were sent to the Unité des Rickettsies, CHU Hôpital de la Timone, Marseille, France for further analysis. The results showed positivity of PCR[1] for spotted fever group rickettsiosis and for *R. africae* on biopsy (Table 1).

Table 1
Results of microbiological and serological investigations performed at the Unité des Rickettsies, CHU Hôpital de la Timone, Marseille, France, on different specimens collected from the patient on day 30 after the onset of symptoms

Method	Specimen[a]	Result	Reference value
Cellular culture for *Rickettsia spp*	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for spotted fever group rickettsiosis	Whole blood stored at −80 °C	Negative	Negative
PCR for *Rickettsia africae*	Whole blood stored at −80 °C	Negative	Negative
Serology (IFA) for *Rickettsia conorii*	Serum stored at −80 °C	Negative	Significant titre: IgG ≥128; IgM ≥64
Serology (IFA) for *Rickettsia typhi*	Serum stored at −80 °C	Negative	Significant titre: IgG ≥128; IgM ≥64
Serology (IFA) for *Rickettsia felis*	Serum stored at −80 °C	Negative	Significant titre: IgG ≥128; IgM ≥64
Serology (IFA) for *Rickettsia africae*	Serum stored at −80 °C	IgG 64, IgM 0	Significant titre: IgG ≥128; IgM ≥64
PCR for *Bartonella spp*	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for *Borrelia spp*	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for spotted fever group rickettsiosis	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	POSITIVE	Negative
PCR for *Francisella tularensis*	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for *Coxiella burnetii*	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for *Staphylococcus aureus*	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for *Streptococcus pyogenes*	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for *Treponema pallidum*	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for *Orthopoxvirus*	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for *Parapoxvirus*	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative
PCR for *Rickettsia africae*	Cutaneous biopsy stored at −80 °C	POSITIVE	Negative
PCR for 16S RNA	Cutaneous biopsy with formalin	Negative	Negative
	Cutaneous biopsy stored at −80 °C	Negative	Negative

PCR, polymerase chain reaction; IFA, indirect immunofluorescence.
[a] Cutaneous biopsy refers to biopsy of the lesion compatible with 'tache noire'.

Thirteen days after admission, urination normalized and the indwelling catheter was removed. In the following days, the faecal incontinence, anal hypertonia, and vulvar oedema resolved. The patient was discharged 1 month after admission; she was still on pregabalin, oxycodone/naloxone, and oral prednisone.

After discharge the patient experienced a severe relapse of left sciatic pain with paroxysmal exacerbations when she discontinued the prednisone, despite still being on pregabalin and oxycodone/naloxone. Pregabalin and oxycodone/naloxone were discontinued and a new course of high-dose corticosteroids combined with carbamazepine was prescribed, achieving progressive pain control.

The patient was able to resume work activities only 4 months after the onset of symptoms, and she was still taking low-dose corticosteroids and carbamazepine at that time. On neurological examination, the Lasègue sign had regressed, but a slight reduction of the left Achilles reflex persisted. No motor or sensory deficit was observed, nor was sphincter dysfunction reported by the patient.

3. Discussion

Previous reports have already mentioned the possibility of neurological involvement in the course of ATBF. Jensenius et al. suggested that nuchal stiffness and neck muscle pain in patients with ATBF reflect a transient central nervous system infection.[2] Jackson et al. reported a significant mood disorder (irritability and depressed mood) in two out of seven patients in a series of cases.[3] Jacquemard et al. reported positive *R. africae* serology associated with severe encephalopathy in a small series of paediatric patients in South Africa.[4] Peripheral nervous system involvement at 3 to 6 weeks following ATBF has been reported only in a case series describing six patients with sub-acute neuropathy.[5] The manifestations reported in these series were radiating pain, paresthesia, and/or motor weakness of the extremities in three cases, hemifacial pain and paresthesia in two cases, and neurosensory hearing loss in one case.

In these cases, an immune-mediated mechanism appeared to be the most likely, given the typical time lag preceding the infection to the onset of neurological symptoms, the development of neurological complications despite the correct treatment for the preceding ATBF, and the lack of response of the neurological symptoms to treatment with doxycycline.[5] However the authors stated that the prompt institution of anti-rickettsial therapy may be crucial, since neurological manifestations developing after other types of rickettsiosis have been reported to improve rapidly with adequate antimicrobial treatment.

In our case we diagnosed a painful sacral syndrome with a pathogenesis that appeared to be related to both direct damage induced by *R. africae* and an immune-mediated mechanism.

The possibility of a direct role of *R. africae* is supported by the fact that neurological disorders were present from the onset of the disease and the sciatic pain was located in the same leg on which the ‘tache noire’ was present. However, the severe relapse of pain after stopping prednisone and a complete course of doxycycline suggests a persistent inflammation no longer sustained by the infectious agent, but most likely immune-mediated.

Funding: None declared.

Ethical considerations: Written informed consent for publication was obtained from the patient.

Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. Update on tick-borne rickettsioses around the world: a geographic approach. *Clin Microbiol Rev* 2013;**26**:657–702.
2. Jensenius M, Fournier PE, Vene S, Hoel T, Hasle G, Henriksen AZ, et al. African tick bite fever in travelers to rural sub-Equatorial Africa. *Clin Infect Dis* 2003;**36**:1411–7.
3. Jackson Y, Chappuis F, Loutan L. African tick-bite fever: four cases among Swiss travelers returning from South Africa. *J Travel Med* 2004;**11**:225–8.
4. Jacquemard R, Pretorius AM, van der Ryst E, Venter A, Kelly PJ. Severe encephalopathies in children with antibodies reactive with *Rickettsia africae*. *S Afr Med J* 1998;**88**:1432.
5. Jensenius M, Fournier PE, Fladby T, Hellum KB, Hagen T, Prio T, et al. Sub-acute neuropathy in patients with African tick bite fever. *Scand J Infect Dis* 2006;**38**:114–8.